Journal of Orthopaedic Surgery and Research

RESEARCH ARTICLE **Open Access**

Is intercalary frozen autograft augmented with intramedullary cement and bridging plates fixation a durable reconstruction?

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Abstract

Aims We analysed the survival, complications, and function of frozen autograft augmented with intramedullary cement and bridging plates fixation for intercalary bone defect reconstruction in primary bone sarcomas.

Patients and Methods A retrospective cohort study was conducted on 72 patients with primary bone sarcomas (34 males, 38 females) between January 2016 and June 2023. The average age was 22.0 ± 13.6 years (6 to 61 years) and the pathological type included osteosarcoma (55), followed by adamantinoma (5), Ewing's sarcoma (4), undifferentiated pleomorphic sarcoma (4), chondrosarcoma (3), and malignant tenosynovial giant cell tumor (1). The oncological outcomes included local control, metastasis, progression-free survival and overall survival. The functional outcomes were evaluated by the Musculoskeletal Tumor Society Score (MSTS-93), the Toronto Extremity Salvage Score (TESS), and the motion of the joint.

Results The mean follow-up time was 50.0 ± 27.4 months (12 to 99 months). 10 patients died of the disease, 9 patients were alive with disease and 53 patients were alive with no evidence of disease. The average 5-year overall survival of autograft was 85.8% (95% CI, 72.1-93.1%). The average MSTS-93 score was 96% (67–100%) and the average TESS score was 98% (74–100%). Twenty-four patients (33.3%) had at least one complication in the follow-up period. The most common complications were nonunion (9.7%, 7/72) and local recurrence (9.7%, 7/72), followed by leg length discrepancy (6.9%, 5/72), infection (5.6%, 4/72), implant failure (4.2%, 3/72), delayed union (2.8%, 2/72), and graft fractures (1.4%, 1/72). Tumor site was an independent risk factor for bone nonunion (OR, 22.23; $p = 0.006$).

Conclusions We presented a large technique series for preventing autograft-related complications (especially for autograft fractures) of intercalary frozen autograft reconstruction. This method showed promising functional outcomes and provided durable reconstruction.

Level of evidence level IV therapeutic study.

Keywords Intercalary frozen autograft, Intramedullary cement, Bridging plates, Function, Complications

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Introduction

For bone tumours located in the diaphysis and metaphysis of long bones, intercalary resection and reconstruction is an ideal procedure as it preserves the native joint and ligaments and provides better proprioception and a more normal function [1]. Intercalary reconstruction techniques have been widely reported, including intercalary endoprostheses, allografts, inactivated autografts, allograft prosthetic composites (APC), vascularised fibula and its composites, distraction osteogenesis and Masquelet techniques [2–11]. Endoprostheses provide immediate stability and weight bearing, however, the incidence of mechanical complications and long-term failure is quite high [2]. Allografts require bone banking and have a high incidence of fracture, infection and nonunion [7].

Inactivated autograft is a reconstructive technique mainly used in Japan, China, and in the developing countries, while biological reconstruction is now favoured to allograft and autograft in US, UK, and Europe, particularly when the resection involves major joints [12–16]. The advantages of recycled autografts include no need for bone banking, no transmission of viral or bacterial diseases and the ability to reattach preserved soft tissues and ligaments [16]. Several methods for tumour bone inactivation are available, including autoclaving, external irradiated autografts, absolute ethanol inactivation, liquid nitrogen inactivated autografts, and pasteurised autografts [5, 17–19]. However, infection and graft fracture are the most common complications of frozen autografts [20]. Previous studies have reported that intramedullary bone cement can reduce the incidence of complications and graft failures in intercalary allografts, but few reports were found in intercalary inactivated autograft augmentation reconstruction [21].

This study aims to analyse the effect of intramedullary bone cement combined with bridging plates in recycled inactivated autografts and to answer the following questions: (1) What is the overall survival rate of frozen autografts augmented with intramedullary bone cement combined with bridging plate fixation? (2) What is the complication rate of frozen autograft augmented with intramedullary bone cement combined with bridging plate fixation according to the modified Henderson classification? (3) What is the function of frozen autograft augmented with intramedullary bone cement combined with bridging plate fixation?

Table 1 The general demographics of all patients

Variable	Total (*n*, %)
No.	72
Size (mean, cm)	17.9 ± 6.2 (9–34)
Gender	
Male	34
Female	38
Age (mean, years)	22.0 (6–61)
Tumor types	
Osteosarcoma	55 (76%)
Adamantinoma	5 (7%)
Ewings Sarcoma	4 (6%)
UPS	4 (6%)
Chondrosarcoma	3 (4%)
Malignant TGCT	1 (1%)
Grade	
Low	48 (23%)
High	121 (58%)
Reconstructed section	
Metadiaphyseal	52 (72%)
Diaphyseal	20 (28%)
Chemotherapy	
Yes	55 (76%)
No	17 (24%)
Radiotherapy	
Yes	9 (12%)
No	63 (88%)
Follow-up (mean, months)	50.0 ± 27.4 (12–99)

UPS = undifferentiated pleomorphic sarcoma; TGCT = tenosynovial giant cell tumor

Materials and methods

We retrospectively reviewed the clinical data of 85 patients who underwent intercalary frozen autograft reconstruction which was prospectively collected at our institution between January 2016 and July 2023 (Table 1). This study was approved by the Ethics Committee of Beijing Jishuitan Hospital. Patients who underwent intercalary frozen autografts augmented with intramedullary bone cement and bridging dynamic compression plates and were followed up for at least 1 year were included in the study. Eight patients (9.4%) were excluded due to loss of follow-up or incomplete datasets. Five patients (5.9%) were excluded because they received intramedullary nailing fixation.

The demographic data of all patients are shown in Table 2. There were 34 males and 38 females. The mean age at diagnosis was 22.0 ± 13.6 years (6 to 61 years). The diagnosis of all patients was confirmed by preoperative biopsy pathology. The most common pathological type was osteosarcoma (55 cases), followed by adamantinoma (5 cases), Ewing's sarcoma (4 cases), undifferentiated pleomorphic sarcoma (4 cases), chondrosarcoma (3 cases), and malignant tenosynovial giant cell tumour (1 case). Thirty-nine cases were located in the femur, 26 in the tibia, and 7 in the humerus. The mean length of curvilinear reconstruction was 17.9 ± 6.2 cm (9 to 34 cm). Fifty-two cases involved the metaphysis and 20 only the diaphysis. Fifty-six patients were treated with chemotherapy. Nine patients were treated with radiotherapy.

The surgical technique has been described in our previous study [22]. After en-bloc resection of the tumour, the

Table 2 All complications and causes of autograft removal

Complications	Femur, *n* (%)	Tibia, *n* (%)	Humerus, *n* (%)
Nonunion	1 (14.3%)	1 (14.3%)	5 (71.4%)
Recurrence	4 (57.1%)	3 (42.9%)	0 (0.0%)
Infection	3 (75.0%)	1 (25.0%)	0 (0.0%)
LLD	3 (60.0%)	2 (40.0%)	-
Implant failure	0 (0.0%)	1 (33.3%)	2 (66.6%)
Delayed union	1 (50.0%)	1 (50.0%)	0 (0.0%)
Fracture	0 (0.0%)	1 (100.0%)	0 (0.0%)

attached soft tissue was excised and the intramedullary contents were removed using a reamer or curette. We use a 4-mm-diameter Stern's needle to perforate the cortex along the long axis of the bone at intervals of 2 cm to prevent fracture during liquid-nitrogen freezing. The bone was immersed in liquid nitrogen for 30 min, thawed at room temperature (25 ℃) for 15–20 min, and rewarmed in saline for 15 min. Antibiotic bone cement was then filled into the medullary cavity of the frozen bone using a bone cement gun and the bone cement should be 0.5 cm away from the osteotomy site, ensuring full contact between host-graft bone junction. Subsequently, the frozen autograft is reconstructed using dynamic compression plates and the length of the plate should span the autografts. Generally, one plate is used for the upper extremities and two for the lower extremities (Figs. 1 and 2). The bridging plates were fixed with at least 4 screws at the host bone and no additional bone grafting was used in the initial procedure.

The primary study endpoint in this study was cumulative graft survival, and graft failure was defined as graft removal for any reason. The secondary study endpoint was the complication rate, and complications were recorded according to the modified Henderson classification proposed by the International International Society for Limb Salvage [23]. Union time of metaphyseal and diaphyseal osteotomy sites were recorded. Bone union was confirmed when more than 75% of the cortex at the junction bridged to the frozen graft at the host bone diaphysis in both X-ray views (AP or lateral view) or any CT plane. Delayed union was defined as union 2 years after surgery. Nonunion was defined as no partial bony junction between host bone and grafts 2 years postoperatively or additional surgery for promoting union at the graft-host junction. The graft fracture was defined as a fracture away from the graft-host bone junction. We used the Musculoskeletal Tumor Society score (MSTS-93) and the Toronto Extremity Salvage Score (TESS) score to evaluate the function, and function was assessed only in patients who retained their frozen bone implants at the last follow-up [24, 25]. Sixty-two patients were available for functional evaluation at the last follow-up.

Statistical analysis

The Kaplan-Meier method and log-rank test were used to analyse autograft overall survival, including revision for any reason and removal of autograft as endpoints indicating failure. The data was evaluated with SPSS version 26.0 (IBM Corp, Armonk, New York) and GraphPad Prism software version 10 (USA). A two-sided $p<0.05$ was considered statistically different.

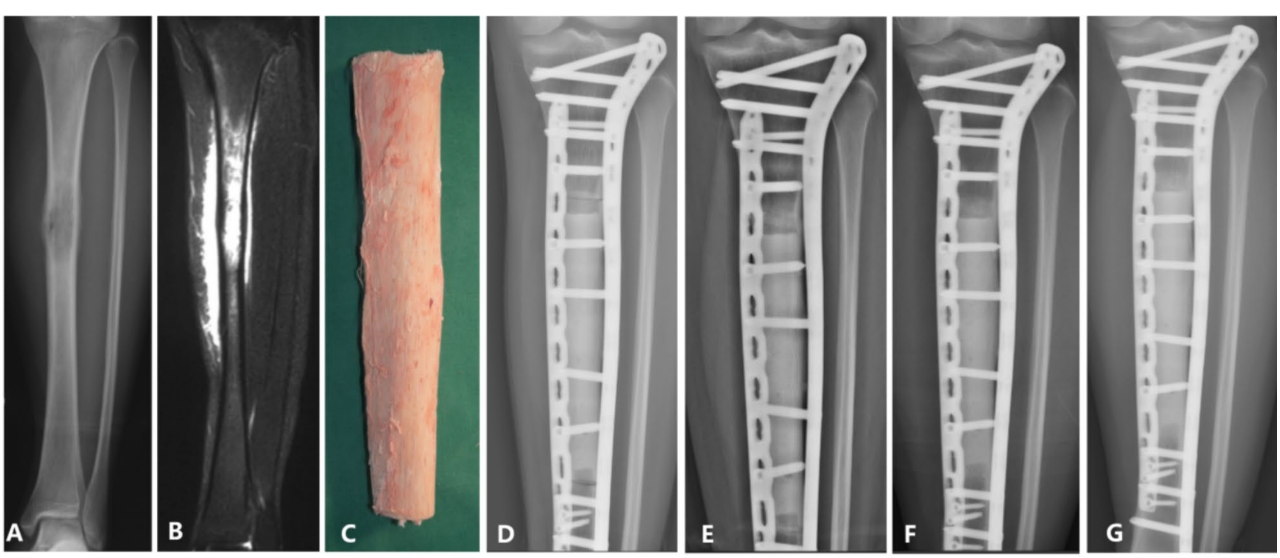

Fig. 1 A 16-year-old female with osteosarcoma of the left tibia. **(A-B)** X-ray and T2-weighted MRI showed tumor was located in the left tibial diaphysis. **(C-D)** The autogenous bone was inactivated in liquid nitrogen. **(E)** Immediate postoperative image shows bridging plate fixation combined with intramadullary cement. **(D)** At 3 months postoperatively, the proximal and distal osteotomy sites began to unit. **(E)** At 12 months postoperatively, both the proximal and distal osteotomy lines had well had excellent consolidation. **(F-G)** Five years after surgery, the autograft is still in good condition

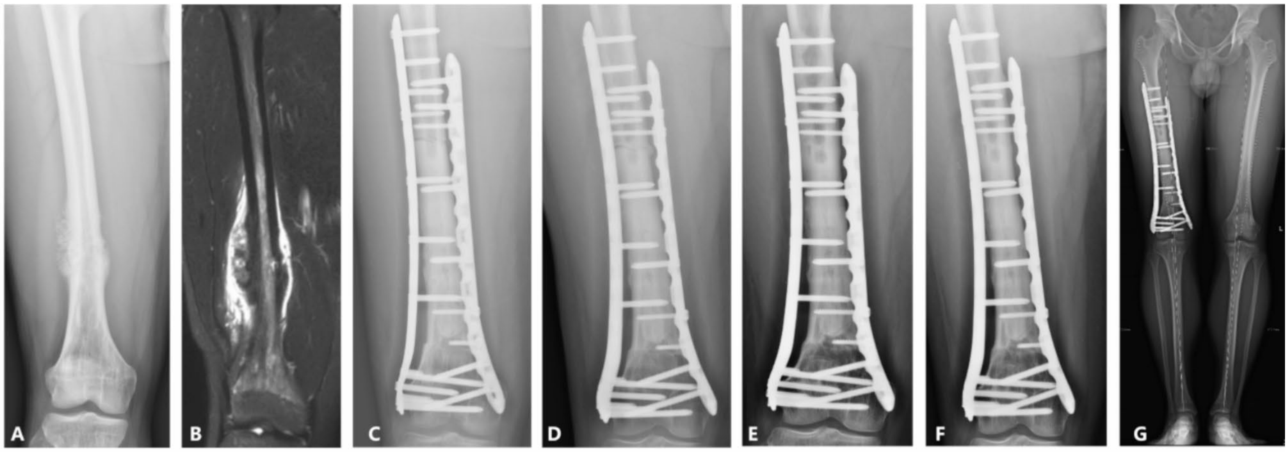

Fig. 2 A 15-year-old male with osteosarcoma of the right femur. **(A-B)** X-ray and T2-weighted MRI showed the tumor involvement in the right femoral diaphysis. **(C)** Immediate postoperative image bridging plate fixation combined with intramadullary cement. **(D)** At 3 months postoperatively, the proximal and distal osteotomy lines began to unit. **(E)** At 12 months postoperatively, both the proximal and distal osteotomy lines are well integrated. **(F-G)** Five years after surgery, the autograft is still in good conditions

Results

The mean follow-up time was 50.0±27.4 months (12 to 99 months). 47% (34/72) of patients were followed up for more than 5 years. At the last follow-up, 10 patients died of the disease, 9 patients were alive with evidence of disease and 53 patients were alive with no evidence of disease. Seven patients had local recurrence and 18 patients had distant metastases (11 lung metastases, 4 lung and bone metastases, and 3 bone metastases). Of the seven patients with local recurrence, five patients had soft-tissue recurrences and two patients had host-bone recurrences. The autografts were removed in six patients for local recurrence. Three patients underwent hip disarticulation and three patients underwent endoprosthetic replacement. One patient underwent resection of musculus vastus lateralis and had a re-recurrence at 15 months postoperatively, followed by quadriceps resection, with no recurrence at the final follow-up.

The 5-year overall survival rate for frozen autografts was 85.8% (95% CI, 72.1–93.1%; Fig. 3). Of the 7 patients who had complications leading to implant removal, 6 cases were due to local recurrence and one was the deep infection. 33.3% (24/72) of patients had at least one complication. The most common complications were nonunion (29.2%, 7/24) and local recurrence (29.2%, 7/24), followed by leg length discrepancy (20.8%, 5/24), infection (16.6%, 4/24), implant failure (12.5%, 3/24), delayed union (8.3%, 2/24), and graft fractures (4.2%, 1/24). By reconstruciton sites, non-mechanical complications (Type IV and Type V) occurred mainly in the femur (6/11, 54.5%) and tibia (4/11, 36.4%), and nonunion occurred mostly in the humerus (5/7, 71.4%). No structural failure difference was found between the upper and lower extremities.

In four patients who had the postoperative infection, three patients had superficial infection and accepted debridement. While one patient had deep infection and autograft was then removed, antibiotic spacers and intravenous antibiotics were used before further reconstruction was carried out. The endoprosthetic reconstruction was performed after the infection was controlled. Five patients had leg length discrepancy (LLD), however no cases had surgical indications. All patients with LLD accepted conservative treatment using shoe lifts. One patient had with a distal tibial fracture due to external violence, therefore the patient underwent cast immobilisation and the fracture united after 3 months of conservative treatment.

Of the 7 nonunion cases, 5 cases were located in the humerus, 1 case in the femur and 1 case in the tibia (Fig. 4). There were 52 metaphyseal and 92 diaphyseal osteotomy sites. Nonunion occurred in 9 osteotomy sites. 77.8% (7/9) of nonunion cases occurred in the diaphyseal and 22.2% (2/9) of nonunion cases occurred in the metaphyseal osteotomy sites. Five (71.4%) of nonunion cases were sixteen years of age and older. Both nonunion cases in the lower extremities underwent revision surgery. However, only one patient accepted secondary autologous bone grafting. Multivariate logistic regression showed tumor site (humerus) was an independent risk factor for bone nonunion (OR, 22.23; $p=0.006$).

For the 62 patients available for functional evaluation, the mean MSTS-93 score was 96% ± 6% (67–100%) and the TESS score was 98% ± 4% (74–100%). Pain and emotional acceptance scores ranged from 4 to 5. Function, support, walking and gait scores ranged from 2 to 5. Regarding knee function, the mean active flexion angle was 131° (80° to 140°). For shoulder function, the mean

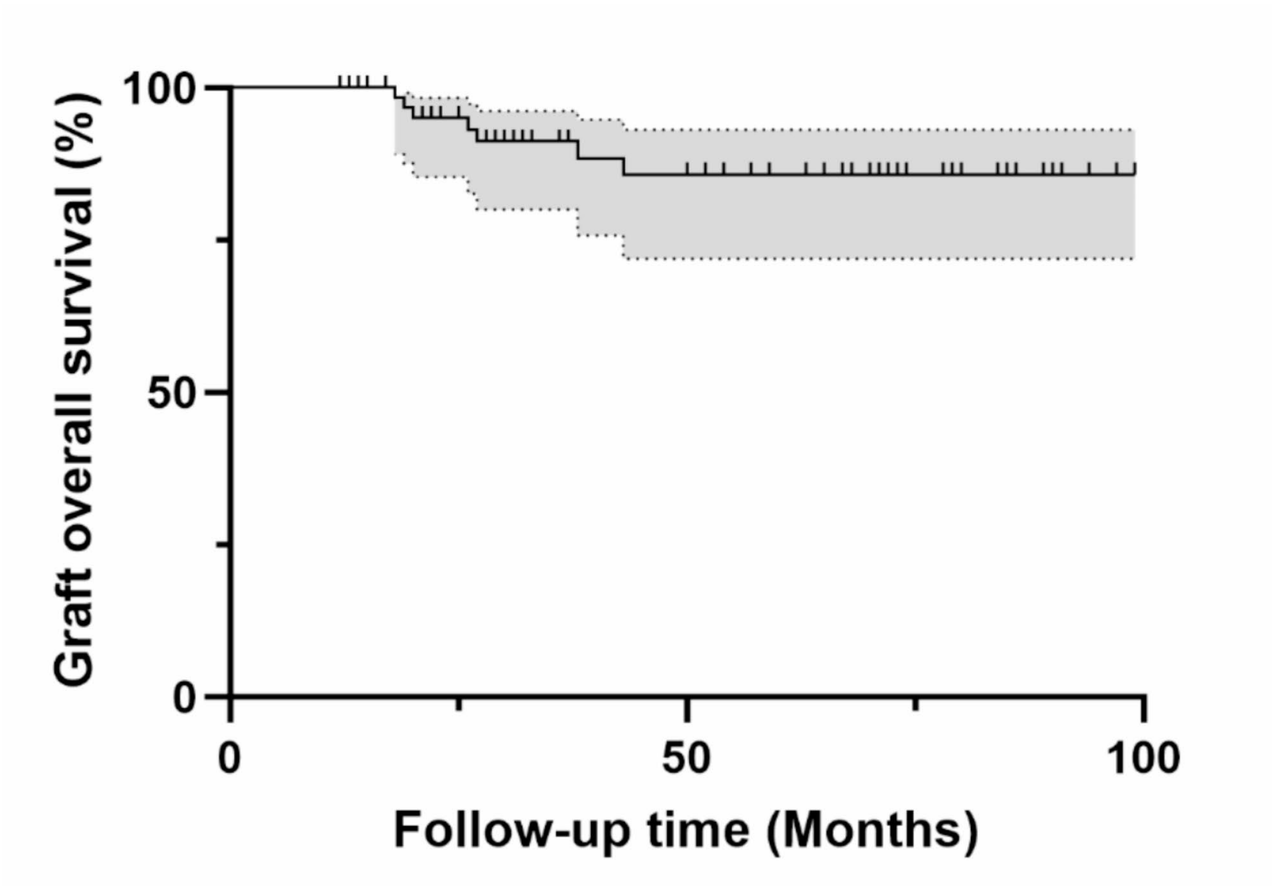

Fig. 3 Kaplan-Meier curve showed the overall survival of frozen autografts

active flexion angle was 170° (120° to 180°) and the mean active abduction angle was 168° (90° to 180°).

Discussion

Reconstructive techniques for intercalary bone defects have been widely reported, including intercalary endoprostheses, inactivated autografts, massive allografts, vascularised fibula, distraction osteogenesis and Masquelet technique. Endoprosthetic reconstruction is the most common reconstruction method worldwide. However, there is a high incidence of mechanical complications (18-57%) and long-term implant failures for endoprosthetic reconstruction [2]. Allograft reconstruction is a widely used biologic reconstruction technique, which also has a high mechanical complication rate (25-73%) and may require vascularised fibula to improve outcomes [7, 26, 27]. Inactivated autograft is a less costly and well-matched biological reconstruction. Due to economic, religious, and cultural reasons, Inactivated autografts are widely used in East and Southeast Asian countries [4, 8, 15, 18, 28–30].

Previous studies have reported several methods of tumour bone inactivation and reimplantation, including autoclaving, absolute ethanol inactivation, external irradiation, liquid nitrogen inactivation, and pasteurisation [12–16]. Takeuchi recently described that liquid nitrogen inactivated, irradiated, and pasteurized autografts had similar rates of complications, graft survival and similar limb function (survival: freezing: 88%; irradiation: 83%; and pasteurisation: 88%) [8]. Several previous studies have reported frozen autografts can retain more osteoinductive capacity, which may lead to better bone union after reconstruction [31–36]. Marcove et al. firstly described cryosurgery for the palliative treatment of primary and metastatic bone tumours [37]. Tsuchiya et al. firstly described the clinical outcomes of liquid nitrogen-inactivated autografts for bone defect reconstruction, with an infection rate of 11%, a fracture rate of 7% and a nonunion rate of 7% [4]. Our institution used absolute ethanol inactivation for autograft reconstruction before 2015, with a high complication rate (graft fracture 20.4%, infection 20.4%, nonunion 17.3%, and implant failure 7.9%), and the 5-year survival rate of inactivated bone was only 55% [38]. Therefore, we used liquid nitrogen inactivation for autograft reconstruction after 2015. Our previous study reported preliminary results of liquid

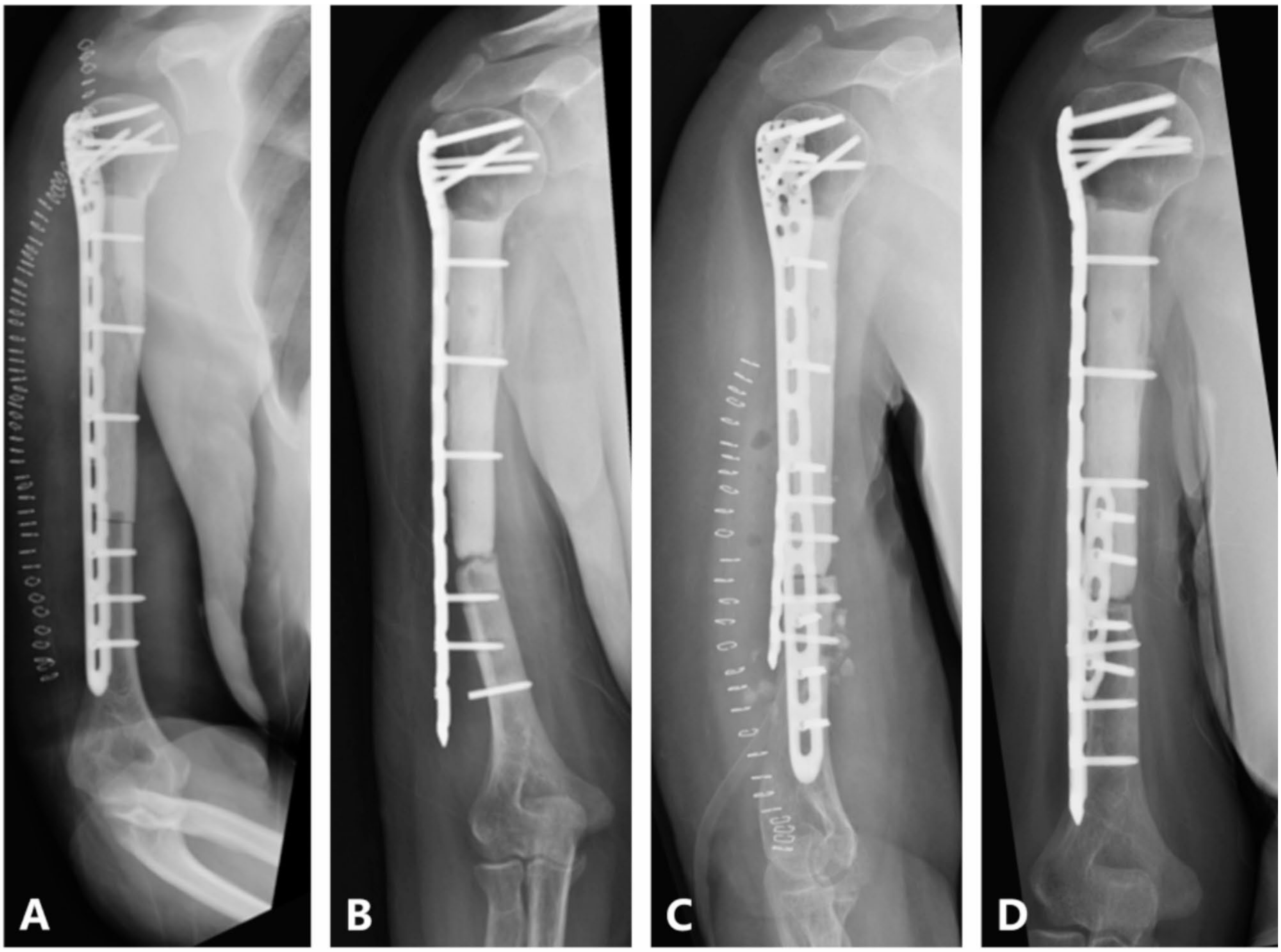

Fig. 4 A 48-year-old female underwent resection of humeral osteosarcoma and reconstruction of frozen autograft. **(A)** Immediate postoperative AP radiograph showed bridging plate fixation combined with intramedullary cement. Osteotomy lines can be easily identified. **(B)** At 14 months postoperatively, There is persistent pseudarthrosis of the distal autograft-host junction and the screw fractured. **(C)** Autologous bone grafting and additional plate fixation were performed at the distal graft-host bone junction. **(D)** AP radiographswere made 30 months after the initial procedure and the union of the distal osteotomy line was still not seen. The patient rejected reoperation because of the acceptable joint function of the upper extremity

nitrogen-inactivated autografts, with a total complication rate of 14.3% and no autograft was removed [22].

The 5-year overall survival rate of frozen autografts reported in this study was 85.8%, which is comparable to previously reported graft survival rates (80–89%) [39–45]. Miwa et al. reported a 5-year frozen autograft survival rate of 88.8% for plate fixation, while the 5-year survival rate of frozen autografts was 71.1% for intramedullary nailing fixation [46]. A systematic review by Huang et al. reported 362 allografts for risk factors of reconstruction failure and found that intramedullary nailing fixation alone had a significantly higher rate of nonunion than plate fixation (OR=2.2, 95% CI: 1.23 to 4.10) and the risk of fracture was lower for frozen autografts than allografts (OR=0.3, 95% CI, 0.14 to 0.64) [20]. The most common mode of autograft failure in previous studies was infection, followed by local recurrence. The most common mode of autograft failure in this study was local recurrence (85.7%, 6/7), followed by infection (14.2%, 1/7). We believed that the possible reason may be bone cement combined with bridging plates reduced the incidence of deep infection and mechanical complications, while the predominance of high-grade sarcomas (77.8%) of this cohort resulted in a higher percentage of local recurrences.

The complication rate of frozen autograft reconstruction in this study was 33.3% (24/72), which was comparable with previous studies [40–44]. Ozaki et al. firstly reported the reconstructive outcomes of 26 intramedullary cement-augmented allografts and 19 noncement-augmented allografts. 15.8% (3/19) of noncement-augmented allografts had autograft fractures and no fractures occurred in cement-augmented allografts [47]. 21.1% of noncement-augmented and 3.8% of cement-augmented allografts had deep infection. Gupta et al. used intramedullary bone cement combined with locking plates for the reconstruction of intercalary allografts and had a graft fracture rate of 4.3% (2/46) and a deep infection rate of 8.6% (4/46) [21]. Wisanuyotin et al. reported on a biomechanical analysis of the augmentation effect of bilateral locking plates with different configurations on femoral allografts and found that a dual lateral-medial LP with bone cement augmentation providing the strongest fixation of the femur in terms of axial compression and lateral bending stiffness [48]. Our results support this conclusion and only one patient (1.4%) had graft fracture, which is lower than former studies [20, 39, 42–44].

Yang et al. reported the results of 33 intercalary frozen autograft reconstructions with a total complication rate of 28.1% (fracture rate, 6.1%) and a mean MSTS-93 score of 87.2% (70–100%) [39]. Tian et al. presented a fracture incidence of 62.5% (10/16) in periprosthetic frozen autograft reconstructions about the knee, and eight cases had knee dislocations [49]. Intramedullary cement augmented fixation combined with bridging plates was not used in 9 out of 10 fracture cases, and we believe that the lack of plate reconstruction or a strong internal fixation is responsible for the high fracture incidence. Takeuchi et al. reported gender and the use of intramedullary nailing only was an independent risk factor for bone nonunion. Our study showed reconstruction site (humerus) was an independent risk factor for bone nonunion. We believed that the use of unilateral bridging plate fixation only in the upper extremity does not provide enough fixation, which may increase the risk of upper extremity nonunion. Moreover, 39 cases were skeletally immature patients in our study. For cases where the osteotomy line was located in the metaphysis, the incidence of LLD was 12.8%, but no severe LLD (≥4 cm) was found. All patients were treated conservatively with shoe lifts. For patients with severe LLD, distraction osteogenesis may be an acceptable treatment choice for leg lengthening [11].

The mean MSTS-93 score in this study was 96% with good active mobility of the knee and shoulder. Such excellent functional results may be related to the preservation of the surrounding joint muscle attachment points and ligaments. However, this study only assessed functional outcomes in patients who retained frozen bone grafts at the last follow-up and did not consider functional outcome scores in patients with amputation or revision surgery, which may lead to an overestimation of functional outcomes. Nevertheless, we still believe that intercalary frozen bone grafts are a satisfactory reconstruction. Meanwhile, future studies should focus on comparing the functional outcomes of different reconstruction techniques, such as intercalary endoprostheses, allografts, and inactivated autografts.

There were also some limitations in this study. Firstly, there was inevitable selection bias. The percentage of high-grade osteosarcoma in this study was 77.8% (56/72), which was higher than that reported in previous studies (33–53%). This may be because our institution is a sarcoma referral centre in China and treats more high-grade sarcoma patients. Secondly, the lack of a control group in this study is because our centre almost rarely uses intramedullary nailings and non-bridging plates for inactivated autograft fixation after using intramedullary bone cement combined with bridging plates, which limits comparisons of the results of different reconstruction techniques. Finally, the sample size of this study remains limited. We believe a larger sample size and longer follow-up (≥10 years) are needed to validate the long-term reconstructive effect of frozen autografts.

Author contributions

Concept and design: Weifeng Liu; data collection: Zhiping Deng, Yongkun Yang; drafting of the article: Zhuoyu Li; critical revision of the article: Qing Zhang and Xiaohui Niu. Zhuoyu Li and Zhiping Deng contributed equally to this paper.

Funding

This work was supported by the National Key R&D Program of China Grant No (2023YFB4706300), National Natural Science Foundation of China (62171017), Beijing Natural Science Foundation (L212042), and Beijing Municipal Health Commission (BJRITO-RDP-2024).

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Ethics Review Board of Beijing Jishuitan Hospital. All methods were performed in accordance with the 1964 Declaration of Helsinki and its later amendments, and the ethical standards of the institutional research committee.

Consent for publication

Written informed consent for publication was obtained from all participants.

Competing interests

The authors declare no competing interests.

Received: 5 July 2024 / Accepted: 4 November 2024
Published online: 10 November 2024

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